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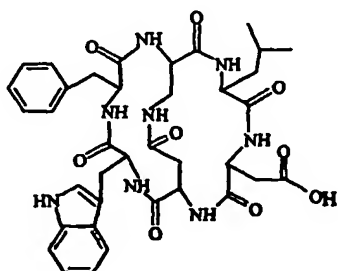
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- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
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- Published:**
— with international search report
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- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR THE PREPARATION OF BICYCLIC HEXA-PEPTIDE NEPADUTANT

Cyclo(Asp(OH)-Asp-Trp-Phe-Dpr-Leu)



(I)

(57) Abstract: The present invention relates to a new process carried out entirely in solution, for the preparation in high yields of high purity bicyclic peptide compounds of formula (I), useful as intermediates for preparing compounds with pharmacological activity.

INTERNATIONAL SEARCH REPORT

tional Application No

03/13696

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07K7/56 C07K1/02 C07K1/06 C07K1/113 C07K7/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WEISSHOFF H ET AL: "Structure determination and by-product profile of the NK2 receptor antagonist nepadutant, a bicyclic glycopeptide"</p> <p>FEBS LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 491, no. 3, 2 March 2001 (2001-03-02), pages 299-304, XP004257321</p> <p>ISSN: 0014-5793</p> <p>the whole document</p> <p style="text-align: center;">--- -/-</p>	1-8, 15-25

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family.

Date of the actual completion of the international search

19 July 2004

Date of mailing of the international search report

09.12.04

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Vogt, T

INTERNATIONAL SEARCH REPORT

ational Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ANISFELD S T ET AL: "A CONVERGENT APPROACH TO THE CHEMICAL SYNTHESIS OF ASPARAGINE-LINKED GLYCOPEPTIDES" JOURNAL OF ORGANIC CHEMISTRY, vol. 55, no. 21, 1990, pages 5560-5562, XP002288954 ISSN: 0022-3263 the whole document	9-25
Y	DAVIS BENJAMIN G: "Synthesis of glycoproteins." CHEMICAL REVIEWS. FEB 2002, vol. 102, no. 2, February 2002 (2002-02), pages 579-601, XP002288955 ISSN: 0009-2665 the whole document	9-25
Y	OFFER J ET AL: "ON-RESIN SOLID-PHASE SYNTHESIS OF ASPARAGINE N-LINKED GLYCOPEPTIDES: USE OF N-(2-ACETOXY-4-METHOXYBENZYL)(ACHMB) ASPARTYL AMIDE-BOND PROTECTION TO PREVENT UNWANTED ASPARTIMIDE FORMATION" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, CHEMICAL SOCIETY. LETCHWORTH, GB, vol. 2, 1996, pages 175-182, XP002055030 ISSN: 0300-922X the whole document	9-25
A	TUCHALSKI, GISBERT ET AL: "Large scale synthesis of biologically active bicyclic hexapeptides" PEPTIDES 1996, PROCEEDINGS OF THE EUROPEAN PEPTIDE SYMPOSIUM, 24TH, EDINBURGH, SEPT. 8-13, 1996 (1998), MEETING DATE 1996, 845-846. EDITOR(S): RAMAGE, ROBERT; EPTON, ROGER. PUBLISHER: MAYFLOWER SCIENTIFIC, KINGSWINFOR, UK., 1998, XP009028177 the whole document	1-8, 15-25
A	WO 96/28467 A (ARCAMONE FEDERICO ;MAGGI CARLO ALBERTO (IT); QUARTARA LAURA (IT);) 19 September 1996 (1996-09-19) cited in the application the whole document	1-8, 15-25

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INTERNATIONAL SEARCH REPORT

ational Application No

101/EP 03/13696

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	AKAJI K ET AL: "Synthesis of MEN11420, a glycosylated bicyclic peptide, by intramolecular double cyclization using a chloroimidazolium coupling reagent" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 57, no. 9, 25 February 2001 (2001-02-25), pages 1749-1755, XP004317634 ISSN: 0040-4020 the whole document	1-25
A	CACIAGLI V ET AL: "LARGE-SCALE PRODUCTION OF PEPTIDES USING THE SOLID-PHASE CONTINUOUS FLOW METHOD. PREPARATIVE SYNTHESIS OF THE NOVEL TACHYKININ ANTAGONIST MEN 10627" JOURNAL OF PEPTIDE SCIENCE, JOHN WILEY AND SONS LTD, GB, vol. 3, no. 3, May 1997 (1997-05), pages 224-230, XP009028229 ISSN: 1075-2617 the whole document	1-8, 15-25

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 03/13696

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: Claims 1-8 and 15-25 (partly).

Process for the preparation of the bicyclic hexapeptide intermediate Cyclo{'Asp-Asp-Trp-Phe-Dpr-Leu! cyclo(2b-5b)}.

Invention 2: Claims 9-14 and 15-25 (partly).

Process for the preparation of the bicyclic hexapeptide nepadutant
Cyclo{'Asn(2-acetamido-2-deoxy-b-D-glucopyranose)-Asp-Trp-Phe-Dpr-Leu! cyclo(2b-5b)} starting from the intermediate Cyclo{'Asp-Asp-Trp-Phe-Dpr-Leu! cyclo(2b-5b)}.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

EP 13696

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